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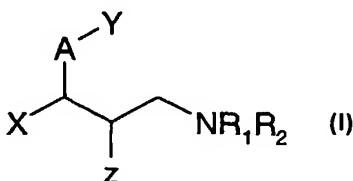
60/424,117 5 November 2002 (05.11.2002) US

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE,

[Continued on next page]

A1 (54) Title: 3-ARYLOXY/THIO-3-SUBSTITUTED PROPANAMINES AND THEIR USE IN INHIBITING SEROTONIN AND NOREPINEPHRINE REUPTAKE

WO 2004/043904



(57) Abstract: There is provided a compound of formula (I) wherein A is selected from -O- and -S-; X is selected from C₂-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₈ cycloalkyl and C₄-C₈ cycloalkylalkyl, each of which may be optionally substituted with up to 3 substituents each independently selected from halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkyl-S(O)_n- where n is 0, 1 or 2, -CF₃, -CN and -CONH₂; Y is selected from phenyl, naphthyl, dihydrobenzothienyl, benzothiazolyl, benzoisothiazolyl, quinolyl, isoquinolyl, naphthyridyl, thienopyridyl, indanyl, 1,3-benzodioxolyl, benzothienyl, indolyl and benzofuranyl, each of which may be optionally substituted with up to 4 or, where possible, 5 substituents each independently selected from halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkyl-S(O)_n- where n is 0, 1 or 2, nitro, acetyl, -CF₃, -SCF₃ and cyano; and when Y is indolyl it may be substituted or further substituted by an N-substituent selected from C₁-C₄ alkyl; Z is selected from H, OR₃ or F, wherein R₃ is selected from H, C₁-C₆ alkyl and phenyl C₁-C₆ alkyl; R₁ and R₂ are each independently H or C₁-C₄ alkyl; with the proviso that, when Z is H, then Y may not be optionally substituted phenyl or optionally substituted naphthyl.

of which may be optionally substituted with up to 4 or, where possible, 5 substituents each independently selected from halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkyl-S(O)_n- where n is 0, 1 or 2, nitro, acetyl, -CF₃, -SCF₃ and cyano; and when Y is indolyl it may be substituted or further substituted by an N-substituent selected from C₁-C₄ alkyl; Z is selected from H, OR₃ or F, wherein R₃ is selected from H, C₁-C₆ alkyl and phenyl C₁-C₆ alkyl; R₁ and R₂ are each independently H or C₁-C₄ alkyl; with the proviso that, when Z is H, then Y may not be optionally substituted phenyl or optionally substituted naphthyl.



DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY,

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- of inventorship (Rule 4.17(iv)) for US only

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- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US03/31514

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C217/64 C07D333/56 A61P25/24 A61P25/18 A61P25/06
A61K31/381 A61K31/137

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T.L. LEMKE: "beta-Adrenergic blocking agents. alpha- and gamma-Methyl(aryloxy)propanolamines" J.MED.CHEM., vol. 24, no. 10, 1981, pages 1211-1214, XP002275394 *p. 1221, compounds 5a-f* -----	1,2,4, 16,17, 39-43
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 30 November 1988 (1988-11-30), XP002275395 Database accession no. BRN: 1463192 AND 1468893 abstract -/-	1,2,8, 32,33, 40-43

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

30 March 2004

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US03/31514

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& MNDZHOYAN ET AL: IZV.AKAD.NAUK.AR.M.SSR.KHIM.NAUKI, vol. 15, 1962, page 185, -----	
Y	EP 0 373 836 A (LILLY CO ELI) 20 June 1990 (1990-06-20) the whole document -----	1-17, 26-31, 39-52
Y	US 5 776 969 A (JAMES STEVEN PARKER) 7 July 1998 (1998-07-07) the whole document -----	1-17, 26-31, 39-52
Y	US 5 023 269 A (ROBERTSON DAVID W ET AL) 11 June 1991 (1991-06-11) the whole document -----	1-17, 26-31, 39-52
P,X	WO 02/094262 A (RATHMELL RICHARD EDMUND ; FAGAN MARIA ANN (GB); GALLAGHER PETER THADDE) 28 November 2002 (2002-11-28) cited in the application the whole document -----	1-17, 26-31, 39-52
A	EP 0 814 084 A (LILLY CO ELI) 29 December 1997 (1997-12-29) the whole document -----	1-17, 26-31, 39-52
A	US 4 229 449 A (MELLONI PIERO ET AL) 21 October 1980 (1980-10-21) cited in the application the whole document -----	1-17, 26-31, 39-52

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 49-52 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 1-15 (in part), 18-25, 32-38 and 39-52 (in part)

Present claims 1-52 relate to an extremely large number of possible compounds/compositions/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/compositions/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds/compositions/methods supported by examples, e.g. compounds in which Y=unsubstituted or substituted phenyl or benzothienyl.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/31514

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 49–52 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1–15 (in part), 18–25, 32–38 and 39–52 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 3/31514

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 0373836	A	20-06-1990	US AT CA DE DE EP JP	4902710 A 102920 T 2005173 A1 68913930 D1 68913930 T2 0373836 A1 2218661 A		20-02-1990 15-04-1994 14-06-1990 21-04-1994 14-07-1994 20-06-1990 31-08-1990
US 5776969	A	07-07-1998	NONE			
US 5023269	A	11-06-1991	US AT AU AU CA CN CY DE DK EG EP GR HK HU IL JP JP KR MX NZ PH PT SG SU ZA	4956388 A 57924 T 591007 B2 8266087 A 1302421 C 87108175 A ,B 1682 A 3765919 D1 664887 A 18230 A 0273658 A1 3001207 T3 69693 A 47561 A2 84863 A 2549681 B2 63185946 A 9603808 B1 9845 A 222980 A 26556 A 86389 A ,B 114992 G 1598865 A3 8709472 A		11-09-1990 15-11-1990 23-11-1989 23-06-1988 02-06-1992 06-07-1988 10-10-1993 06-12-1990 23-06-1988 30-10-1992 06-07-1988 30-07-1992 30-07-1993 28-03-1989 29-03-1992 30-10-1996 01-08-1988 22-03-1996 01-12-1993 28-11-1989 19-08-1992 01-01-1988 29-01-1993 07-10-1990 30-08-1989
WO 02094262	A	28-11-2002	CA EP WO	2445010 A1 1397129 A1 02094262 A1		28-11-2002 17-03-2004 28-11-2002
EP 0814084	A	29-12-1997	AT AU CA DE DE DK EP ES GR HK JP PT WO US	203990 T 3401797 A 2257962 A1 69706000 D1 69706000 T2 814084 T3 0814084 A1 2160894 T3 3037072 T3 1008525 A1 2000513358 T 814084 T 9748698 A1 5912256 A		15-08-2001 07-01-1998 24-12-1997 13-09-2001 04-04-2002 08-10-2001 29-12-1997 16-11-2001 31-01-2002 15-03-2002 10-10-2000 30-11-2001 24-12-1997 15-06-1999
US 4229449	A	21-10-1980	IT IT IT	1111676 B 1160301 B 1160302 B		13-01-1986 11-03-1987 11-03-1987

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US83/31514

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 4229449	A		IT 1101724 B	07-10-1985
			AT 371813 B	10-08-1983
			AT 40679 A	15-12-1982
			AU 525954 B2	09-12-1982
			AU 4332779 A	26-07-1979
			BE 873596 A1	19-07-1979
			BG 61056 B2	30-09-1996
			CA 1128942 A1	03-08-1982
			CH 650245 A5	15-07-1985
			CS 207696 B2	31-08-1981
			CS 9104133 A3	13-05-1992
			CY 1172 A	10-06-1983
			DE 2901032 A1	02-08-1979
			DK 22679 A ,B,	21-07-1979
			FI 790177 A ,B,	21-07-1979
			FR 2442839 A1	27-06-1980
			FR 2430412 A1	01-02-1980
			GB 2014981 A ,B	05-09-1979
			HK 5783 A	08-02-1983
			IE 47727 B1	30-05-1984
			IL 56369 A	31-05-1984
			JP 1504458 C	28-06-1989
			JP 54148739 A	21-11-1979
			JP 63031455 B	23-06-1988
			KE 3243 A	03-12-1982
			MY 1884 A	31-12-1984
			NL 7900412 A ,B,	24-07-1979
			NO 790205 A ,B,	23-07-1979
			NZ 189418 A	16-03-1981
			SE 446727 B	06-10-1986
			SE 7900498 A	21-07-1979
			SI 7910096 A8	31-10-1996
			US 4271160 A	02-06-1981
			YU 9679 A1	31-12-1983
			ZA 7900215 A	26-03-1980
			AT 376964 B	25-01-1985
			AT 419781 A	15-06-1984
			CS 207697 B2	31-08-1981
			MX 9203112 A1	01-07-1992
			SU 980617 A3	07-12-1982
			HU 178214 B	28-03-1982
			SU 944500 A3	15-07-1982